## SCIENTIFIC ABSTRACT OF THE PROTOCOL

Cystic fibrosis (CF), the most common lethal genetic disease in North America, is caused by defects in the cystic fibrosis transmembrane conductance regulator (CFTR) gene. The CFTR gene product is required for regulation of epithelial chloride transport in multiple organs, including the airways. CF lung disease develops gradually over many years as abnormally viscous secretions lead to airways obstruction, infection, inflammation, and fibrosis. It ultimately may lead to respiratory failure, which is the cause of death in more than 90% of CF patients.

Gene therapy for CF lung disease is currently being pursued with adenovirus and liposome-based vectors. Although these vector systems are efficient for expression of CFTR both *in vitro* and *in vivo*, neither one results in stable DNA integration into the target cell. As a result, expression from each of these type of vectors is generally transient in nature. Since long-term expression is likely to be important for interrupting the progression of disease as outlined above, neither of the two current systems would seem to be optimal.

Our group has developed an alternative vector system for CFTR gene transfer based on adeno-associated virus (AAV). AAV vectors can undergo stable DNA integration into the host cell, and AAV-CFTR vectors have been shown to confer stable correction of the physiologic defect in cAMP-mediated chloride secretion when administered to cultured CF bronchial epithelial cells. Furthermore, AAV-CFTR vectors transduce and express recombinant CFTR *in vivo* after delivery to the airway surface of animals. Long-term vector expression, up to 6 months after a single-dose administration, has been observed in a New Zealand white rabbit model.

An additional advantage of AAV vectors is the absence of any wild-type AAV viral coding sequence in the vector construct. Inflammatory reaction as a result of viral gene expression is not a possibility with AAV-CFTR vectors because of their lack of viral genes. Studies in rabbits, mice, rats, and rhesus macaques have all demonstrated that single-dose AAV vector administration does not result in lung inflammation or any other adverse effects, even at doses resulting in high levels of recombinant gene expression.

The current study will include an initial phase I clinical trial of AAV-CFTR vector administered to the nose and bronchial epithelium of adult CF patients with mild lung disease. This will be a dose escalation study in which vector expression and safety will be concurrently assessed at a series of vector doses ranging up to $10^{10}$ particles administered to the nasal epithelium and through a fiberoptic bronchoscope to a single lung lobe. The results of this study will serve to guide dosing in future trials aimed at the prevention and treatment of CF lung disease.